PATENT
Attorney Docket No. EURA-004/00US
(Formerly 451194-101)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Gopi M. Venkatesh et al.

Application No.: 10/713,929 Confirmation No.: 4820

Filed: November 14, 2003 Group Art Unit: 1615

For: MODIFIED RELEASE DOSAGE FORMS OF SKELETAL MUSCLE RELAXANTS Examiner: BARHAM, Bethany P.

DECLARATION UNDER 37 C.F.R. § 1.131

We, Dr. Gopi Venkatesh and James M. Clevenger declare as follows:

1. We are the named inventors of the above-noted application (Ser. No. 10/713,929)

2. We have read and understood the Official Action of January 11, 2008, and in particular the rejection of the pending claims under 35 U.S.C. §103 over the combination of U.S. Publ. No. 2004/0197407 (the '407 application) and U.S. Publ. Nos. 2003/0215496 or 2003/0099711.

3. We understand that the earliest asserted priority date of the '407 application is February 11, 2003, through the priority claim to U.S. Provisional Application Ser. No. 60/446,425.

4. The subject matter of the pending claims of the present application was invented by Gopi Venkatesh and James M. Clevenger (the named inventors) prior to February 11, 2003.

5. Example 3 of the instant application describes the formulation and production of a multiparticulate dosage form of cyclobenzaprine, wherein the cyclobenzaprine is coated on sugar spheres and covered with a water insoluble polymer to produced extended release beads (see paragraph 0045). Figure 4 of the instant application shows the release rate of the finished beads of Example 3 (e.g., **Batch 805-AAA-105**).

6. Exhibit A, dated before February 11, 2003, shows a "Master Formula" sheet documenting the production of the intermediate cyclobenzaprine coated beads used to make **Batch 805-AAA-105**. This intermediate batch (designated **Lot No. 837-AG-034**) comprises:

- "Sugar Spheres" (5475 g) coated with "cyclobenzaprine HCl" (1875 g) from "Acetone, NF 50/50% Ratio" and "USP Purified Water, 50/50% Ratio";
- seal coated with "2.00"% of "Opadry Clear YS-1-7006".

Exhibit B, dated before February 11, 2003, shows a "Master Formula" sheet documenting the actual production of **Batch 805-AAA-105** by coating the intermediate cyclobenzaprine beads of **Lot No. 837-AG-034** with an extended release water insoluble polymer:

- ER coating of **Lot No. 837-AG-034** with "Ethylcellulose 10P Premium (10 cps)" (363.6 g) and "Diethyl Phthalate" (36.4 g) dissolved in "Acetone, NF (98 parts) " and "USP Purified Water (2 parts)". Samples were collected with a coating weight of "10%" (designated **Batch or Lot No. 805-AAA-105**).

Exhibit C, dated before February 11, 2003, shows data for the mean cumulative release rate of cyclobenzaprine over time for "Lot # 805-AAA-105-10" (i.e., 10 wt.% ER coating, Batch 805-AAA-105). The data are identical to that presented in graphical form for the sample designated "10% ER Coating Wt., Batch 805AAA105" in Figure 4 of the instant application and shows that the 10% ER coated beads exhibit a release profile that after 2 hours, no more than about 40% of the total active is released; after 4 hours, from about 40-65% of the total active is released; after 8 hours, from about 60-85% of the total active is released; and after 12 hours, from about 75- 85% of the total active is released, wherein said dosage form is dissolution tested using United States Pharmacopoeia Apparatus 2 (paddles @ 50 rpm) in 900 mL of 0.1N HCl at 37°C. This is the same dissolution profile required by the pending claims.

7. Exhibit D, dated before February 11, 2003, is a batch record showing the ingredients of "Cyclobenzaprine HCl ER Beads", **Lot No. PE271EA001**:

- "Cyclobenzaprine HCl Intermediate Beads", Item code **PE249**; coated with "Ethylcellulose" and "Diethyl Phthalate".

Exhibit E, dated before February 11, 2003, documents the manufacture of "Cyclobenzaprine HCl MR Capsules, 30 mg", **Lot No. PF306EA001**:

- "White, Opaque Hard Gelatin Capsules, Size 4", filled with "Cyclobenzaprine HCl Extended Release Beads", Item code **PE271**.

Exhibit F, dated before February 11, 2003, shows data for the mean cumulative release rate of cyclobenzaprine over time for clinical batch "Lot # PF306EA001". The data are identical to that presented in graphical form for the clinical sample designated "PF306EA001" in Figure 6, Examples 4 and 5 of the instant application. Formulation PF306EA001 shows a release profile that after 2 hours, no more than about 40% of the total active is released; after 4 hours, from about 40-65% of the total active is released; after 8 hours, from about 60-85% of the total active is released; and after 12 hours, from about 75- 85% of the total active is released, wherein said dosage form is dissolution tested using United States Pharmacopoeia Apparatus 2 (paddles @ 50 rpm) in 900 mL of 0.1N HCl at 37°C. This is the same dissolution profile required by the pending claims.

8. Thus, Exhibits A and B document the production of the identical multi-particulate cyclobenzaprine dosage forms described in Example 3 of the present application, and as set forth in the instant claims, before February 11, 2003.

9. Thus, Exhibits D and E document the production of the identical clinical batch described in Examples 4 and 5 of the present application, and as set forth in the instant claims, before February 11, 2003.

10. We further declare that all statements made herein on our own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that

such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

Respectfully submitted,

G.M. Venkatesh — 2/13/2008

Gopi Venkatesh — Date

James M. Clevenger — 2/13/2008

James M. Clevenger — Date

Master Formula

Page ——— of ———

Product Name: Cyclobenzaprine HCl, Drug Layered Beads	**Batch Number:** 837AG034		**Date:** [redacted]
Physical Description: Off White	**Capsule Size:** N/A		**Batch Size:** 7500.0 gms
Imprint (Uppers): N \ A	**Imprint (Lowers):** N \ A	**Label (mg \ Unit):** N/A	**Unit Weight (mg):** N/A
Written By: A.Gallo	**Reviewed By:**	**Room #:** 492	**Temperature:** 16.0 °C	**Humidity:** 72.0 %	**Time:** 7:20 AM

ITEM #	Ingredients (Trade Name Grade)	Raw Material Lot #	Quantity %	Quantity Mg \ Unit	Quantity Gm \ batch	Quantity Weighed	Weighed By	Checked By	Date Weighed
1	*Cyclobenzaprine HCl	C14607401	25.00	7.50	1875.0 gm	1875.0	[illegible]		[redacted]
2	Sugar Spheres 20 – 25 Mesh (Hansen)	RD – 991114	73.00	21.90	5475.0 gm	5475.0	[illegible]		
3	**Opadry Clear YS – 1 – 7006	H10507376	2.00	0.60	150.0 gm	150.0	[illegible]		
4									
5.									
6									
7									
8									
9									
10	Acetone, NF 50/50 % Ratio	A10707332			2812.50 ml	2812.50	[illegible]		
11	USP Purified Water, 50/50 % Ratio	W-10002061B			2812.50 ml	2812.50	[illegible]		
12	USP Purified Water @ 10.0 % of Seal Coat	W-10002061B			1350.0 ml	1350.0	[illegible]		
	Total:		100.00	30.00	7500.0 gm	7500.0	[illegible]		

Objective: to evaluate dose @ 25.0 % Using GPCG 5

Note: Acetone, NF / USP Purified Water 50/50 Ratio.

* Item #10,11, 12 is use to make coating solutions. Both mg\ unit and g\ batch totals do not reflect entries.

Exhibit A

Exhibit B

Project No._____

TITLE CYCLOBENZAPANE HCl EC BEADS. Book No. 805

From Page No. 104

Purpose: To EC coat Cyclobenzapine HCl drug layered beads using Solvent (90:10) Acetone : H_2O as a medium. The drug layered beads were then Ethyl Cellulose coated using Acetone : H_2O (98 : 2). The EC was done using Glatt GPCG-5 Wurster.

Master Formula

Product Name: Cyclobenzaprine HCl – Extended Release Beads (25.0 mg)

Physical Description : Extended Release Coating

Lot # 805-AAA-105

Date : [redacted]

Item #	Ingredients (Trade Name Grade)	Raw Material Lot #	Quantity % W\W	Quantity Mg\Unit	Quantity Gm\batch	Quantity Weighed	Weighed By	Checked By
1.	Cyclobenzaprine HCl, Drug Layered Beads	837-AG-034	3600.0			3600.0	AAA	
2.	Ethylcellulose 10P Premium (10cps), NF	B11407226	363.6			364.0	AAA	
3.	Diethyl Phthalate, USP	D11807500	36.4			36.4	AAA	
10.	Acetone, NF (98 parts)	A10707332	5639.0			5639.0	AAA	
11.	Purified Water, USP (2 parts)	W100-01	115.0			115.0	AAA	
	Total:							

Objective: Evaluating Dose @ 10.0 % Samples were taken @ 7, 8., 9, & 10% of EC applied.

Anthony A-Agyi

AAA [redacted]

To Page No

Witnessed & Understood by me, _____ Date [redacted]

Invented by Anthony A-Agyi Date [redacted]

Exhibit C

Project No. —

TITLE Cyclobenzaprine HCl Uniformity Book No. 891

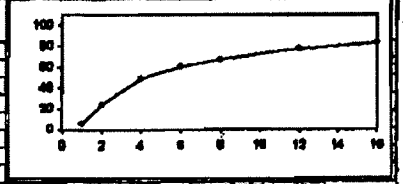
From Page No. 112

[redacted]

Stability Condition:	N/A		Std 2 Dilution (mL):	1000			
Reference:	NB891,P104		Std 2 Conc. (mg/mL):	0.03043			
			Std. = 0.03046 mg/mL				
Vessel	Weight (mg)	Active Wt (mg)	Actual Assay:	22.1			
1	140.85	31.15					
2	141.86	31.35					
3	142.03	31.39					
4	138.28	30.76					
5	141.04	31.17					
6	140.07	30.96					

Info	Area	Std Avg.	(%) Released	Avg. (%) Release	σ_{n-1}	(%) RSD	Spec.	Pass/Fail
Std 1	525679							
1.1	39087		6	6	0.5	9.1	FIO	FIO
1.2	37341		6					
1.3	31848		5					
1.4	31505		5					
1.5	34693		6					
1.6	33750	(Std 142)	6					
Std 2	524333	524106						
2.1	149590		25	24	1.0	4.2	NMT 40%	PASS
2.2	151998		25					
2.3	136383		23					
2.4	135862		23					
2.5	146873		25					
2.6	148717	(Std 283)	25					
Std 3	523652	523983						
4.1	291002		49	48	1.5	2.8	30% - 80%	PASS
4.2	283005		49					
4.3	277113		46					
4.4	274032		47					
4.5	293105		49					
4.6	287012	(Std 384)	49					
Std 4	524619	524126						
6.1	363326		61	60	1.4	2.3	FIO	FIO
6.2	364004		60					
6.3	351458		58					
6.4	340831		58					
6.5	364481		61					
6.6	356000	(Std 485)	60					
Std 5	526539	526679						
8.1	409548		68	67	1.5	2.3	60% - 90%	PASS
8.2	410539		68					
8.3	395003		65					
8.4	387491		65					
8.5	406278		68					
8.6	405270	(Std 586)	68					
Std 6	526956	527098						
12.1	469066		78	77	1.2	1.5	FIO	FIO
12.2	463710		77					
12.3	456203		76					
12.4	448242		75					
12.5	468754		78					
12.6	458622	(Std 687)	77					
Std 7	525680	526268						
16.1	504503		84	83	1.0	1.2	NLT 75%	PASS
16.2	504335		84					
16.3	491652		82					
16.4	483636		82					
16.5	501954		84					
16.6	501349	(Std 788)	84					
Std 8	526741	526211						

Sample	Time	Avg. Rel'd (%)	RSD
005-AAA-105-10	1.0	6	9.1
N/A	2.0	24	4.2
	4.0	48	2.8
	8.0	60	2.3
	8.0	67	2.3
	12.0	77	1.5
	16.0	83	1.2



[redacted]

** For System Suit
See p. 114

% Released = ((50.8349)/(524.211)) (0.03043 mg/mL) (900mL) (100) / (1140.07 mg) (99.1%/100%)

= 84.3%

= 84.4%

Chromatograms stored in Box 891

To Page No. 113

Witnessed & Understood by me,

Dan Hensley

Date [redacted]

Invented by —

Recorded by VMegroz

Date [redacted]

[redacted]

ISSUED BY Q.A.

Eurand America, Inc.
Cyclobenzaprine HCl ER Beads
Batch Size: 85 kg (Theoretical)
MF #: A-50PE271-A

Lot #: PE271EA001	Date of Manufacturing: [redacted]
Effective Date: [redacted]	
Prepared By:	Date: [redacted]
Mfg. Approval By:	Date:
R&D Approval By:	Date:
QA Approval By:	Date:
QA Issue:	Date:
QA Audited By:	Date:

Item No.	Item Code	Bead Dosage (mg/g)	% per Batch (w/w)	Ingredient Name	Theoretical Quantity Per Batch**
1	PE249	910.00	91.00	Cyclobenzaprine HCl Intermediate Beads	77.4 Kg
2	E114	81.25	8.13	Ethylcellulose, Premium Std 10cps	6.9 Kg
3	D118	8.75	0.88	Diethyl Phthalate, NF	0.75 Kg
4	A107 -	—	—	Acetone, NF*	116.7 Kg
5	W100	—	—	Purified Water, USP*	2.4 Kg
		1000.00	100.01	TOTAL=	85.0 Kg

*Removed from process during the drying process
**Actual batch is based on the actual quantity of the Intermediate Beads available for use. See page 2

Exhibit D

ISSUED BY Q.A.

Eurand America, Inc.
Cyclobenzaprine HCl MR Capsules, 30 mg
Batch Size – 130,000 Capsules (Theoretical))
MF#: A-60PF306-A

Lot # PF306EA 001	**Date of Manufacturing:** [redacted]
Effective Date: [redacted]	
Prepared By: James M. Clevenger	**Date:** [redacted]
MFG. Approval By: [signature]	**Date:**
R&D Approval By: M-M-Venkatesh	**Date:**
QA Approval By: Thomas M. Purdy	**Date:**
QA Issue: Thomas M. Purdy	**Date:**
QA Audited By: Thomas M. Purdy	**Date:**

Item Code	Item No.	mg per capsule	% per Capsule (w/w)	Ingredient Name	Quantity per Batch
G134	1	37.00[1]	21.91	White, Opaque Hard Gelatin Capsules, Size 4,	4.81 kg
PE271	2	131.87[2]	78.09	Cyclobenzaprine HCl Extended Release Beads	17.14kg
[redacted]	Total	168.87	[redacted]	[redacted]	21.95 kg

[1]Based on a theoretical empty capsule weight of 37.0 mg

[2]Equivalent to 30 mg of Cyclobenzaprine Hydrochloride (Beads based on a theoretical assay of 22.75%)

Exhibit E

Exhibit F

Cyclobenzaprine 30mg MR Capsules
Lot# PF306EA001

1 hour				Avg. STD
CHKSTD	262100	CHKSTD	256775	259438
1	10845	7	14041	
2	5836	8	14416	
3	12708	9	0	
4	11645	10	14435	
5	11232	11	15293	
6	10460	12	13404	
CHKSTD	256775	CHKSTD	262386	259581

2 hour				
CHKSTD	262386	CHKSTD	263589	262988
1	73230	7	83090	
2	80460	8	86176	
3	80522	9	81274	
4	77577	10	84345	
5	81204	11	78231	
6	80205	12	85540	
CHKSTD	263589	CHKSTD	262191	262890

4 hour				
CHKSTD	262191	CHKSTD	261515	261853
1	135093	7	159208	
2	143494	8	158286	
3	145159	9	151616	
4	143021	10	159810	
5	149228	11	149087	
6	145149	12	160801	
CHKSTD	261515	CHKSTD	266598	265057

6 hour				
CHKSTD	266598	CHKSTD	266252	267425
1	182176	7	197178	
2	191272	8	194560	
3	192435	9	186135	
4	187995	10	197029	
5	195802	11	186727	
6	190502	12	195823	
CHKSTD	266252	CHKSTD	263363	264808

8 hour				Avg. STD
CHKSTD	263363	CHKSTD	270750	267057
1	205885	7	220888	
2	215916	8	218836	
3	216018	9	205793	
4	211804	10	219400	
5	220533	11	211189	
6	214893	12	222248	
CHKSTD	270750	CHKSTD	263356	267053

12 hour				
CHKSTD	263356	CHKSTD	261737	262547
1	232004	7	247658	
2	245230	8	245567	
3	246103	9	230755	
4	245046	10	248980	
5	251569	11	237970	
6	244480	12	252556	
CHKSTD	261737	CHKSTD	261590	261664

10 hour				
CHKSTD	261590	CHKSTD	261252	261421
1	247344	7	264019	
2	262134	8	262718	
3	263693	9	242544	
4	258831	10	265913	
5	268488	11	254822	
6	265056	12	259662	
CHKSTD	261252	CHKSTD	262478	261884

STD conc	0.03007	mg/ml	
Strength	30	mg	

1 hour (FIO)

1	4	7	5
2	2	8	5
3	4	9	0
4	4	10	5
5	4	11	5
6	4	12	5

Average: 4 %

2 hour (0 - 40%)

1	25	7	29
2	28	8	30
3	26	9	28
4	27	10	29
5	28	11	27
6	28	12	29

Average: 28 % Pass

4 hour (30 - 60%)

1	47	7	54
2	49	8	54
3	50	9	52
4	49	10	54
5	51	11	51
6	50	12	55

Average: 51 % Pass

6 hour (FIO)

1	61	7	67
2	65	8	66
3	65	9	63
4	63	10	67
5	67	11	64
6	64	12	66

Average: 65 %

8 hour (60 - 90%)

1	69	7	75
2	73	8	74
3	73	9	70
4	72	10	74
5	74	11	71
6	73	12	75

Average: 73 % Pass

12 hour (FIO)

1	80	7	85
2	84	8	85
3	85	9	80
4	84	10	86
5	86	11	82
6	84	12	87

Average: 84 %

10 hour (NLT 75%)

1	85	7	91
2	90	8	91
3	91	9	84
4	89	10	92
5	93	11	88
6	91	12	93

Average: 90 % Pass